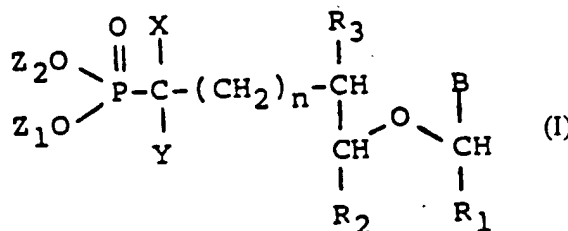


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>3</sup> : C07H 19/10, 19/20; C07F 9/65 A61K 31/70, 31/675	A1	(11) International Publication Number: WO 84/ 04748 (43) International Publication Date: 6 December 1984 (06.12.84)
(21) International Application Number: PCT/US84/00737 (22) International Filing Date: 14 May 1984 (14.05.84) (31) Priority Application Number: 497,720 (32) Priority Date: 24 May 1983 (24.05.83) (33) Priority Country: US (71) Applicant: SRI INTERNATIONAL [US/US]: 333 Ravenswood Avenue, Menlo Park, CA 94025 (US). (72) Inventors: REIST, Elmer, Joseph ; 581 Berkeley Avenue, Menlo Park, CA 94025 (US). STURM, Priscilla, Anna ; 1549 Montalvo Drive, Mountain View, CA 94040 (US). (74) Agent: FAUBION, Urban, H.; SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025 (US).		(81) Designated States: DE, FR (European patent), GB, JP, NL, SE.  Published <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

**FOR YOUR PATENT NEEDS**  
 AML Information Services  
 P.O. Box 405  
 Corte Madera, CA 94925  
 415-927-0340

(54) Title: NOVEL ANTIVIRAL AGENTS



(57) Abstract

Phosphonate analogues of mono-, di-, and triphosphates of antiviral nucleoside analogues. These materials are represented structurally as formula (I), wherein Z<sub>1</sub> and Z<sub>2</sub> are the same or different and selected from the group made up of hydrogen, the one to six carbon alkyls, phenyl and benzyl, X is H, OH, or together with Y = O, Y is H or together with X = O, n is an integer, 0, 2 or 4, R<sub>1</sub> and R<sub>2</sub> together complete a β-pentofuranose sugar or R<sub>1</sub> is H and R<sub>2</sub> is H or -CH<sub>2</sub>OH. R<sub>3</sub> is H or OH and B is a purine or pyrimidine base. These materials have antiviral activity, especially against herpes virus. Antiviral pharmaceutical preparations and their use are disclosed as well.

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	KR	Republic of Korea
AU	Australia	LI	Liechtenstein
BE	Belgium	LK	Sri Lanka
BG	Bulgaria	LU	Luxembourg
BR	Brazil	MC	Monaco
CF	Central African Republic	MG	Madagascar
CG	Congo	MR	Mauritania
CH	Switzerland	MW	Malawi
CM	Cameroon	NL	Netherlands
DE	Germany, Federal Republic of	NO	Norway
DK	Denmark	RO	Romania
FI	Finland	SD	Sudan
FR	France	SE	Sweden
GA	Gabon	SN	Senegal
GB	United Kingdom	SU	Soviet Union
HU	Hungary	TD	Chad
JP	Japan	TG	Togo
KP	Democratic People's Republic of Korea	US	United States of America

NOVEL ANTIVIRAL AGENTS

Field of the Invention

This invention concerns nucleotide analogues and their synthesis and use. More particularly, it concerns phosphonic acid analogues of natural and synthetic nucleoside phosphates and their preparation and use as antiviral agents.

Background of the Invention

There is a recognized need for antiviral agents. Herpes virus hominis alone infects between 50 and 150 million Americans at this time. A number of the antiviral agents that are currently viewed as most effective against herpes are nucleoside analogues. These materials include iododeoxyuridine, 2-hydroxyethoxymethylguanine, 2'-fluoro-5-iodo-1-arabino-furanosyl cytosine and 5-E-bromovinyldeoxyuridine. It is believed that these materials act through their conversion by viral thymidine kinase (but not by host TK) to the nucleotide which is then converted to the triphosphate and incorporated into viral DNA. The incorporation of these analogues into the viral DNA prevents its replication and thus is lethal to the virus. Two shortcomings of this antiviral mechanism have been recognized, however. First, thymidine kinase negative herpes mutants (TK<sup>-</sup>) have been identified which are inherently inactive toward phosphorylating these analogues and thus permitting their incorporation in viral DNA. In addition, TK<sup>+</sup> mutants that are resistant to 2-hydroxyethoxymethyl-guanine have been reported in mice by H. Field, et al, in J Infect Dis, 143 281 (1981). TK<sup>+</sup> mutants resistant to iododeoxyuridine have been reported in



humans by A. Hirano, et al, in Acta Virol 23 226 (1979). It may be that these newly-discovered resistant viral strains do not undergo the monophosphorylation or triphosphate formation needed to permit incorporation in the DNA.

References to these antiviral agents of the art and their use include Am J Med, 73 No 1A, July 20, 1982 "Proceedings of a Symposium on Acyclovir"; Biochem Biophys Acta, 32 295-6 (1959); Antimicrob  
10 Agents Chemother, 578-584 (1965); Science, 145 585-6 (1964); Science, 255 468-80 (1975); J Med Chem, 19 495-8 (1976); Proc Natl Acad Sci, 76 4415-18 (1979); and J Med Chem 22 21-24 (1979).

The present invention provides antiviral  
15 materials which can be lethally incorporated into DNA without the dependence upon enzyme-moderated phosphorylation. The materials of the invention are phosphonate analogues of the mono-, di- and triphosphates of the deoxynucleotide analogs. An article by Robert  
20 Engel appearing at Chem Reviews, 11, #3 pp 349-367 (1977) discusses phosphonate analogues of nucleotides and the like. Other representative references in this area, some of which are cited in the Chem Reviews  
25 article, are German O.L.S 2,350,608 (1974) of Syntex (Jones and Moffatt inventors); German O.L.S. 2,009,834 1970 also of Syntex with Jones and Moffatt as inventors; British Patent 1,243,214 of Syntex, and US Patent 3,560,478 of Myers.

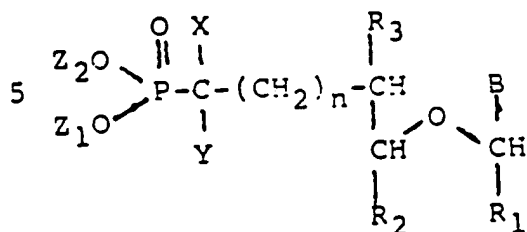
request  
these  
intents. \*

#### Statement of the Invention

30 A group of new materials have now been found. These materials in a broad sense are phosphonate analogues of mono-, di-, and triphosphates of antiviral nucleoside analogues. These analogues



differ from nonlethal natural nucleosides by variations in their sugar ribose moiety and/or by variations in their nucleoside base moieties. Such materials are represented structurally as



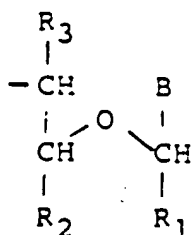
wherein  $Z_1$  and  $Z_2$  are the same or different and selected from the group made up of hydrogen, the one to six carbon alkyls, phenyl and benzyl, X is H, OH, or together with  $Y = O$ , Y is H or together with  $X = O$ , n is an integer, 0, 2 or 4,  $R_1$  and  $R_2$  together complete a  $\beta$ -pentofuranose sugar or  $R_1$  is H and  $R_2$  is H or  $-\text{CH}_2\text{OH}$ ,  $R_3$  is H or OH and B is a purine or pyrimidine base.

In other aspects this invention relates to the preparation of these materials, their formulation into antiviral pharmaceutical compositions and the use of these formulations to treat viral infections, in particular herpes infections.

### Detailed Description of the Invention

#### 20 The compounds

The compounds of this invention are phosphonates which have the structure set forth above in Statement of the Invention.



The unit defines an antiviral nucleoside.

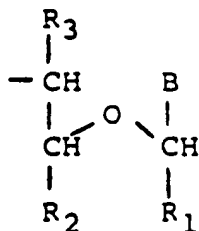
As previously noted, in this structure  $R_1$  and  $R_2$  can together complete a  $\beta$ -pentofuranose sugar.

5 In this configuration they preferably complete a substituted or unsubstituted  $\beta$ -ribofuranose or  $\beta$ -arabinofuranose such as ribose, 2-deoxyribose, 2,3-dideoxyribose, 3-deoxyribose, 2-fluoro-2-deoxyribose or arabinose or the like.

10 In this structure,  $Z_1$  and  $Z_2$  preferably are each selected from hydrogens and one to four carbon alkyls. More preferably  $Z_1$  and  $Z_2$  are each hydrogens. Further in this structure, the integer  $n$  is significant in defining whether the compound is in  
15 size equivalent to a nucleoside monophosphate, a diphosphate or a triphosphate.

Preferred bases include guanine, adenine, 5-iodouracil, 5-trifluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil, 5-propyluracil, and 5-ethyluracil.

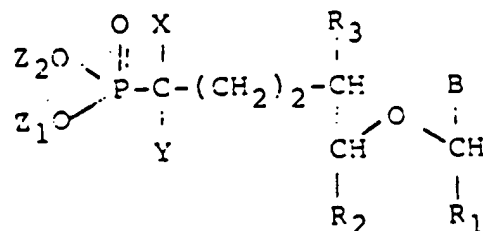
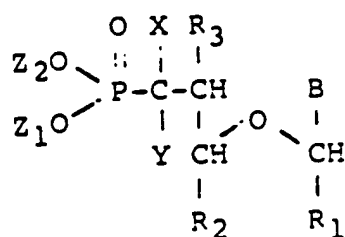
20 Preferred nucleoside analogues (e.g.



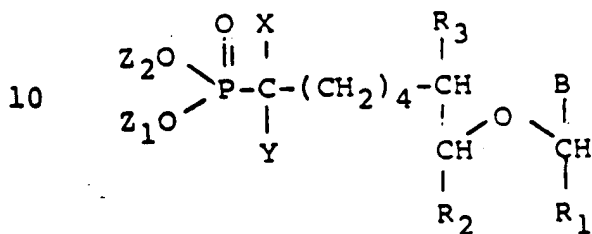
include 5-iodo-2'-deoxyuridine, 9-B-D-arabinofuranosyladenine, 5-trifluorothymidine, E-5-(2-bromovinyl)-2'-deoxyuridine, 1-(2'-deoxy-2'-fluoro-B-D-arabino-

furanosyl)-5-iodocytosine, 5-ethyl-2'-deoxyuridine, 5-propyl-2'-deoxyuridine, 9-(2-hydroxy-ethoxymethyl)guanine, 9-(ethoxymethyl)guanine, 9-(2-hydroxy-ethoxymethyl)adenine and 9-(ethoxymethyl)adenine.

5 These nucleoside analogues yield phosphonates (and di- and triphosphate-phosphonate analogues) having the following general structures



and



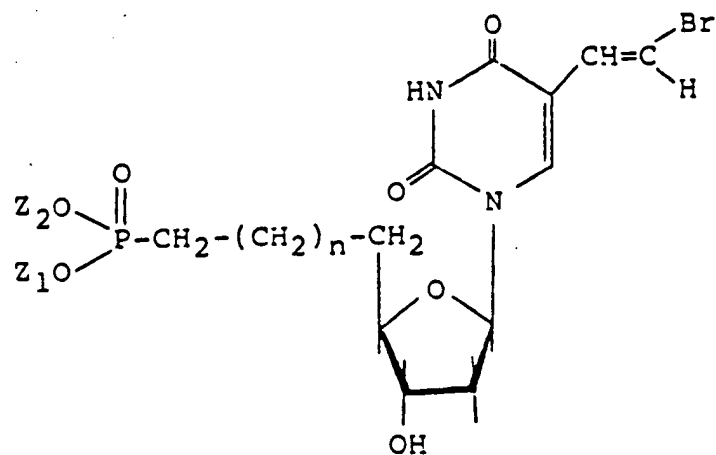
wherein X, Y, Z<sub>1</sub>, Z<sub>2</sub>, B, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as described above. In preferred embodiments, X is hydrogen or hydroxyl and Y is hydrogen. Thus, representative compounds can have the structures shown in Table I.

Table I  
Representative Structures

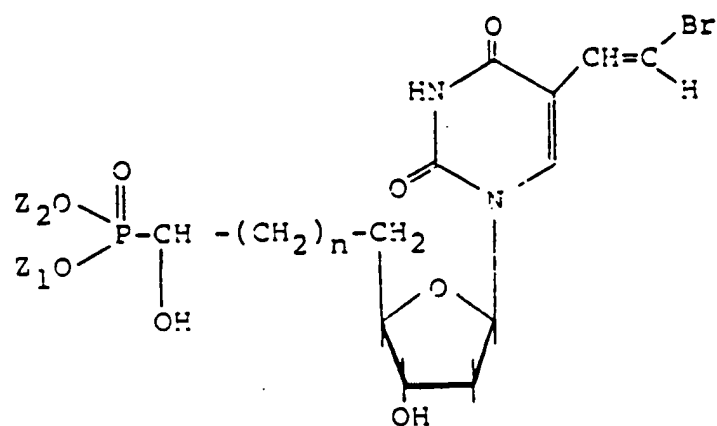
<u>Structure</u>	<u>Structure Number</u>
	1
<p>5</p>	2
	3



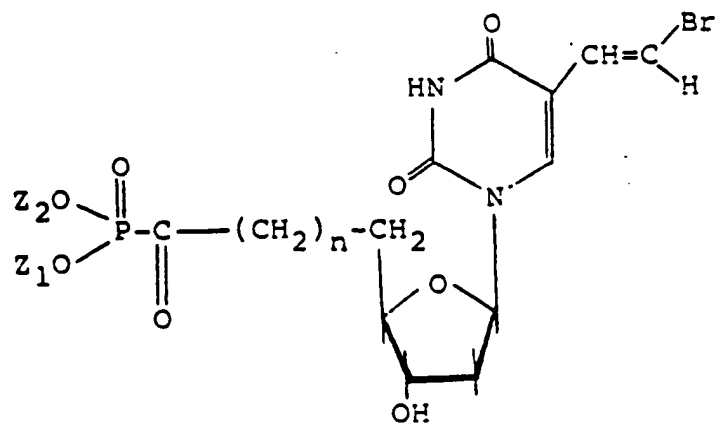
-7-



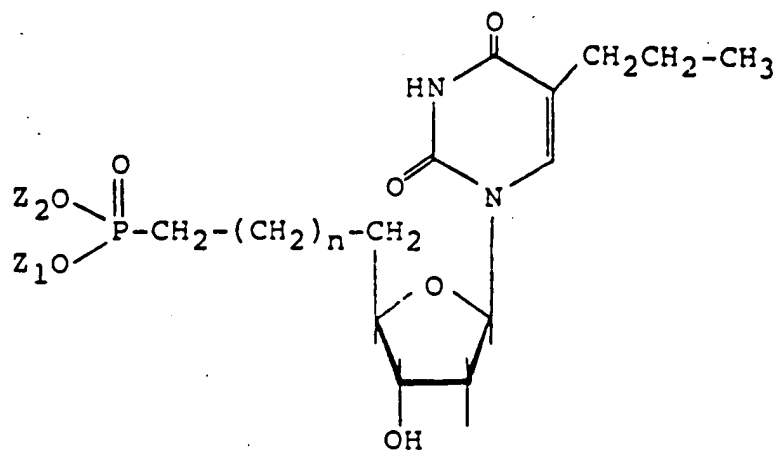
4



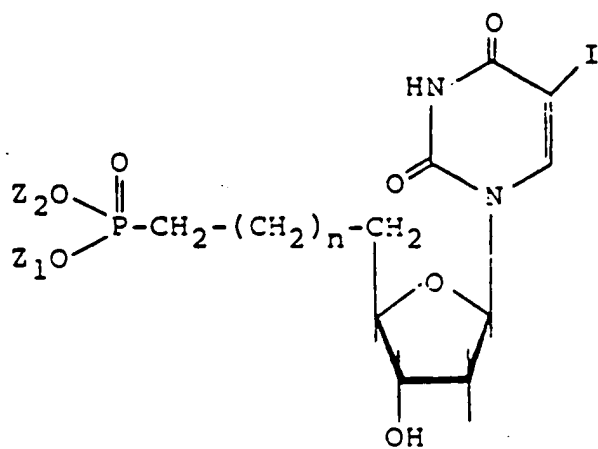
5



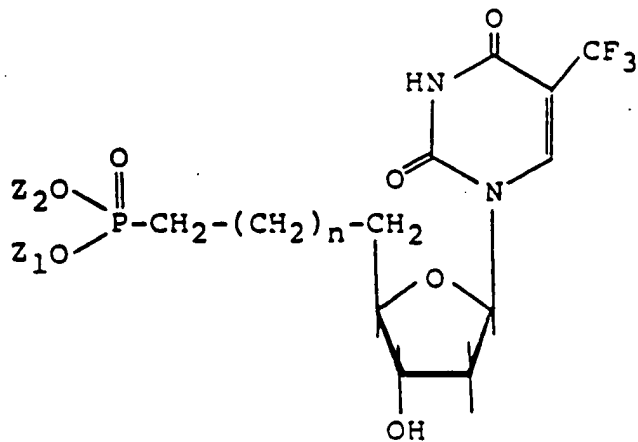
6



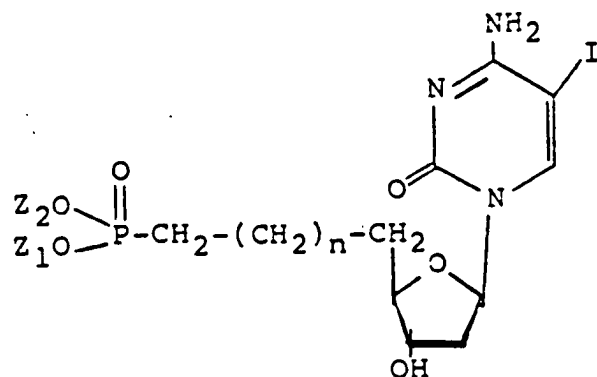
7



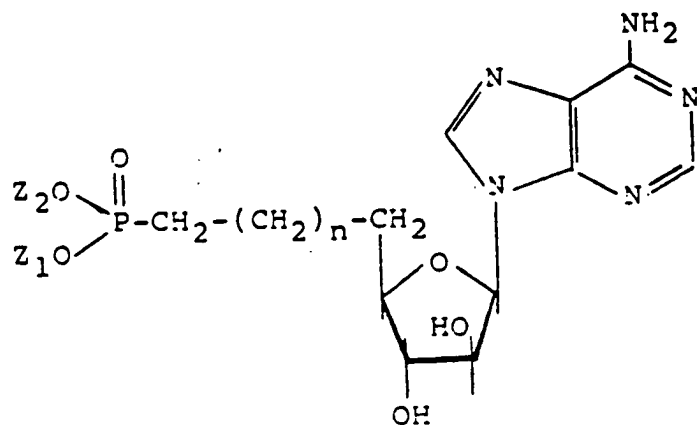
8



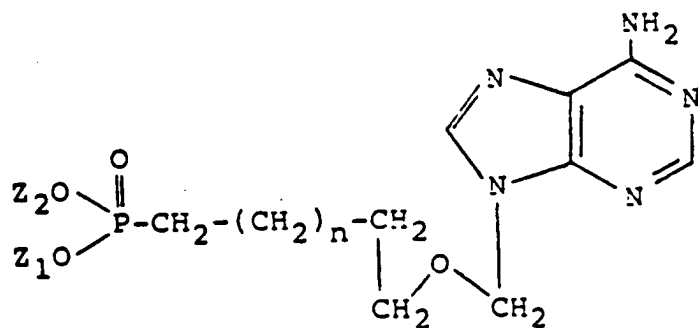
9



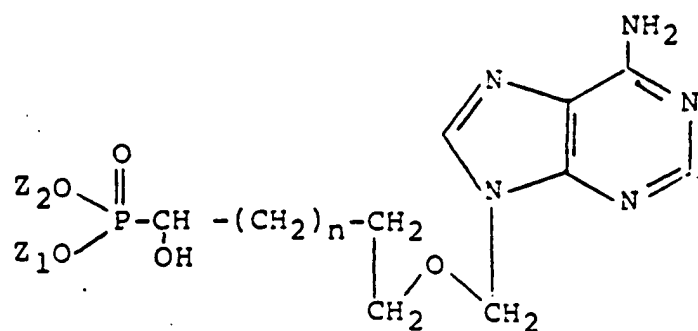
10



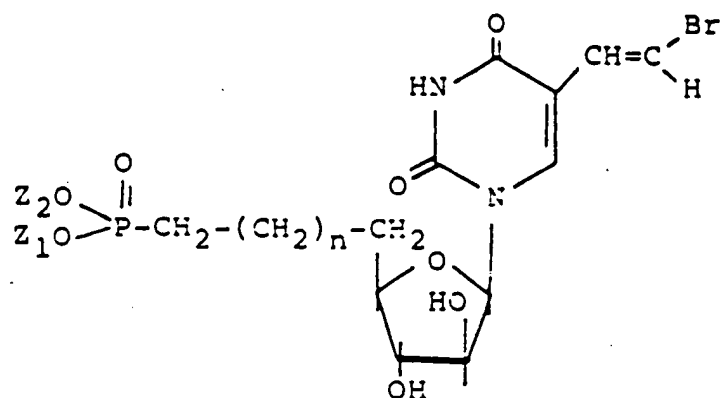
11



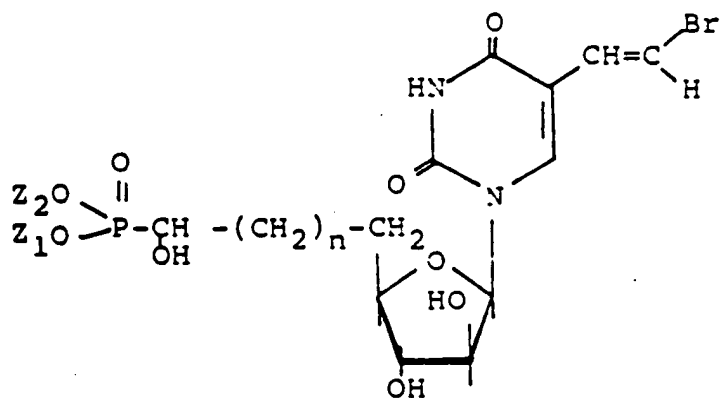
12



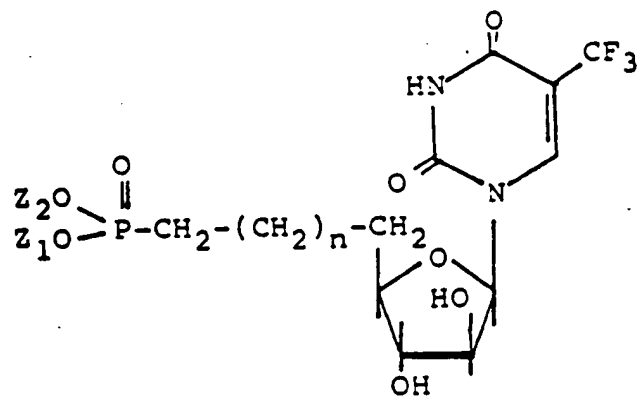
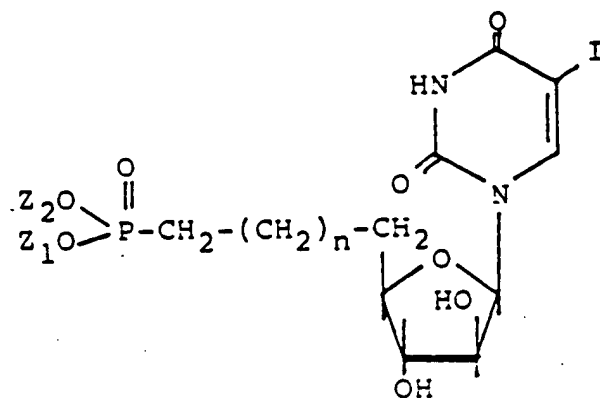
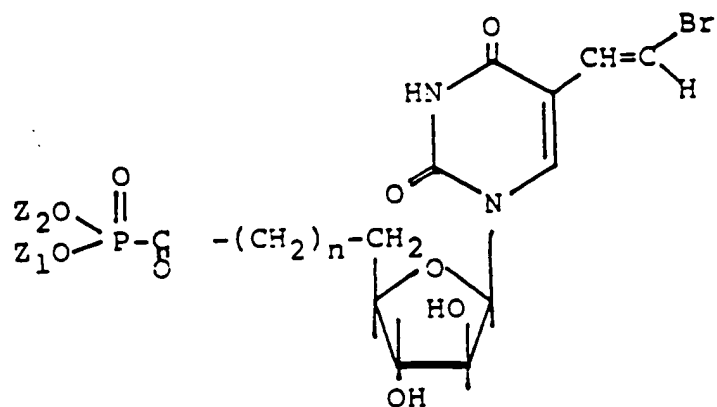
13

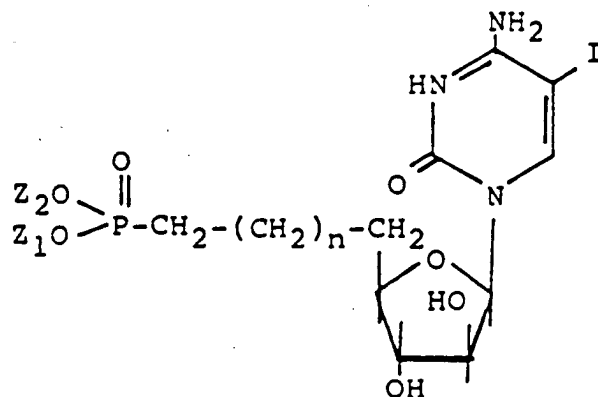


14

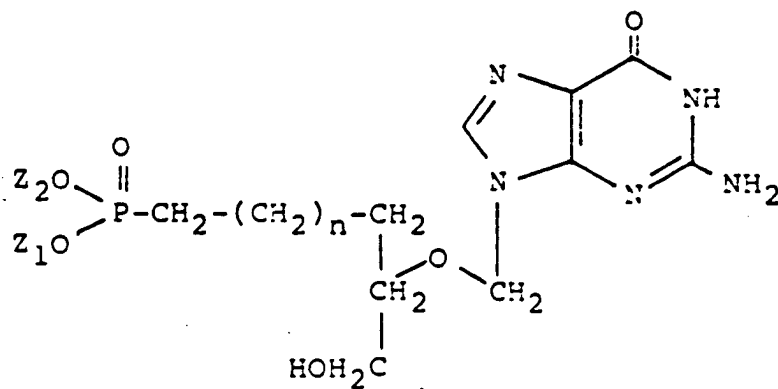


15

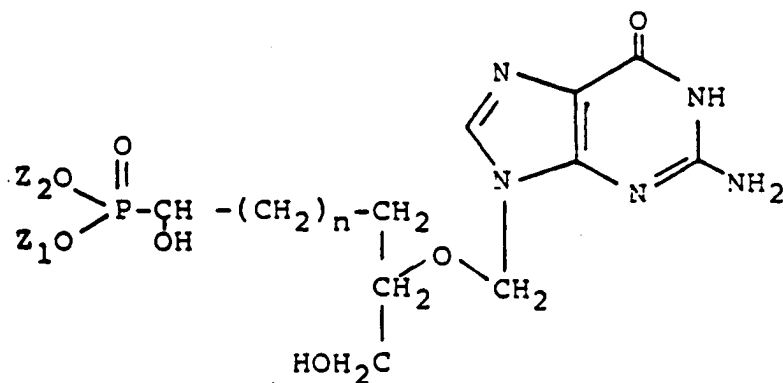




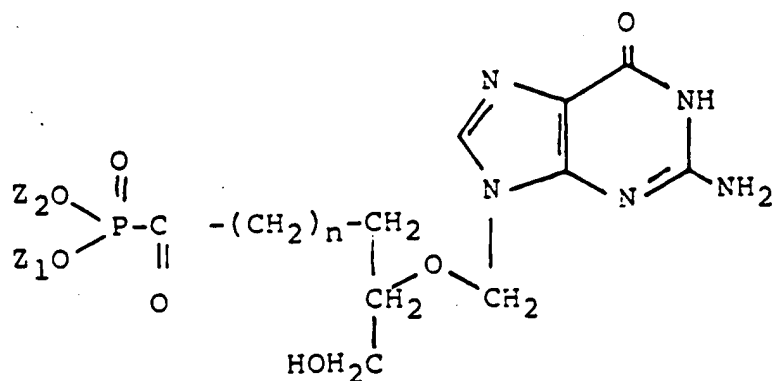
19



20



21



22

Table II  
Representative Compounds  
Monophosphate Analogues

5	Compound Number	Structure Number	Z <sub>1</sub>	Z <sub>2</sub>	n
	1a	1	H	H	O
	1b	1	CH <sub>3</sub>	CH <sub>3</sub>	O
	1c	1	H	CH <sub>3</sub>	O
	1d	1	H	C <sub>2</sub> H <sub>5</sub>	O
10	2a	2	H	H	O
	2b	2	CH <sub>3</sub>	CH <sub>3</sub>	O
	2c	2	H	CH <sub>3</sub>	O
	2d	2	H	C <sub>2</sub> H <sub>5</sub>	O
	3a	3	H	H	O
15	3b	3	CH <sub>3</sub>	CH <sub>3</sub>	O
	3c	3	H	CH <sub>3</sub>	O
	3d	3	H	C <sub>2</sub> H <sub>5</sub>	O
	22a	22	H	H	O
	22b	22	CH <sub>3</sub>	CH <sub>3</sub>	O
20	22c	22	H	CH <sub>3</sub>	O
	22d	22	H	C <sub>2</sub> H <sub>5</sub>	O

Diphosphate Analogs

	<u>Compound Number</u>	<u>Structure Number</u>	<u>Z<sub>1</sub></u>	<u>Z<sub>2</sub></u>	<u>n</u>
5	1e	1	H	H	2
	1f	1	CH <sub>3</sub>	CH <sub>3</sub>	2
	1g	1	H	CH <sub>3</sub>	2
	1h	1	H	C <sub>2</sub> H <sub>5</sub>	2
10	2e	2	H	H	2
	2f	2	CH <sub>3</sub>	CH <sub>3</sub>	2
	2g	2	H	CH <sub>3</sub>	2
	2h	2	H	C <sub>2</sub> H <sub>5</sub>	2
	22a	22	H	H	2
	22b	22	CH <sub>3</sub>	CH <sub>3</sub>	2
	22c	22	H	CH <sub>3</sub>	2
	22d	22	H	C <sub>2</sub> H <sub>5</sub>	2

15

Triphosphate Analogues

	<u>Compound Number</u>	<u>Structure Number</u>	<u>Z<sub>1</sub></u>	<u>Z<sub>2</sub></u>	<u>n</u>
20	1	1	H	H	4
	1	1	CH <sub>3</sub>	CH <sub>3</sub>	4
	1	1	H	CH <sub>3</sub>	4
	1	1	H	CH <sub>3</sub>	4
	22	22	H	H	4
	22	22	CH <sub>3</sub>	CH <sub>3</sub>	4
	22	22	H	CH <sub>3</sub>	4
	22	22	H	C <sub>2</sub> H <sub>5</sub>	4

25

These are merely representative compounds as it will be apparent to those skilled in the art that other combinations of substituents and bases could be employed as well.

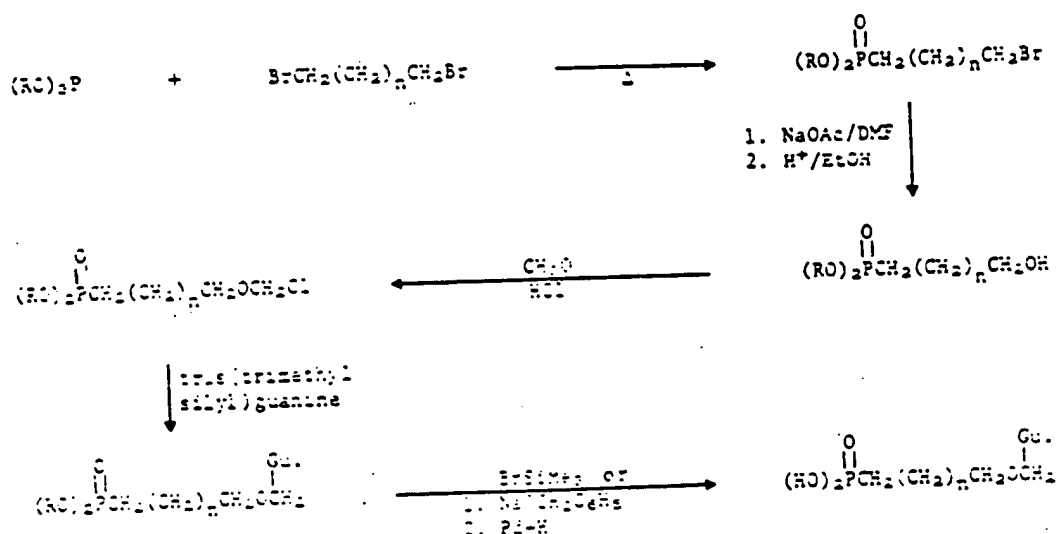




# Preparation

The compounds of this invention can be prepared by the following general procedures: The non  $\beta$ -pentofuranose materials such as materials having structures 1, 2, 12, 13, 20, 21, and 22 in Table I can be made with the representative reaction sequence I.

I.



Scheme I

In this sequence, a trialkyl ( $\text{C}_2$ ,  $\text{C}_4$  or  $\text{C}_6$ ) phosphite reacts with a dibromoalkane in an Arbuzov reaction to give the bromoalkyl phosphonate (See J Am Chem Soc, 87 (2), 253 (1965)). (All cited references are incorporated herein).

Displacement of the bromide using sodium acetate in DMF followed by hydrolysis of the acetate ester gives diethyl 3-hydroxypropylphosphonate (i.e. in sequence I,  $\text{R} = \text{C}_2\text{H}_5$ ,  $n = 1$ ). This material is chloromethylated to the chloromethylester and then reacted with a suitably protected base such as tris-trimethylsilylguanine by the method of Kelley, et al,

J Med Chem, 24 1523 (1981). This yields the phosphono product, e.g. 9-(3-phosphonopropylloxymethyl)guanine, directly. Phosphonate esters are smoothly cleaved by bromotrimethylsilane to the phosphonic ester by the  
5 method of McKenna, et al, Tet Letts, 155 (1977).

The syntheses of a representative deoxy-riboside is illustrated in Scheme II.

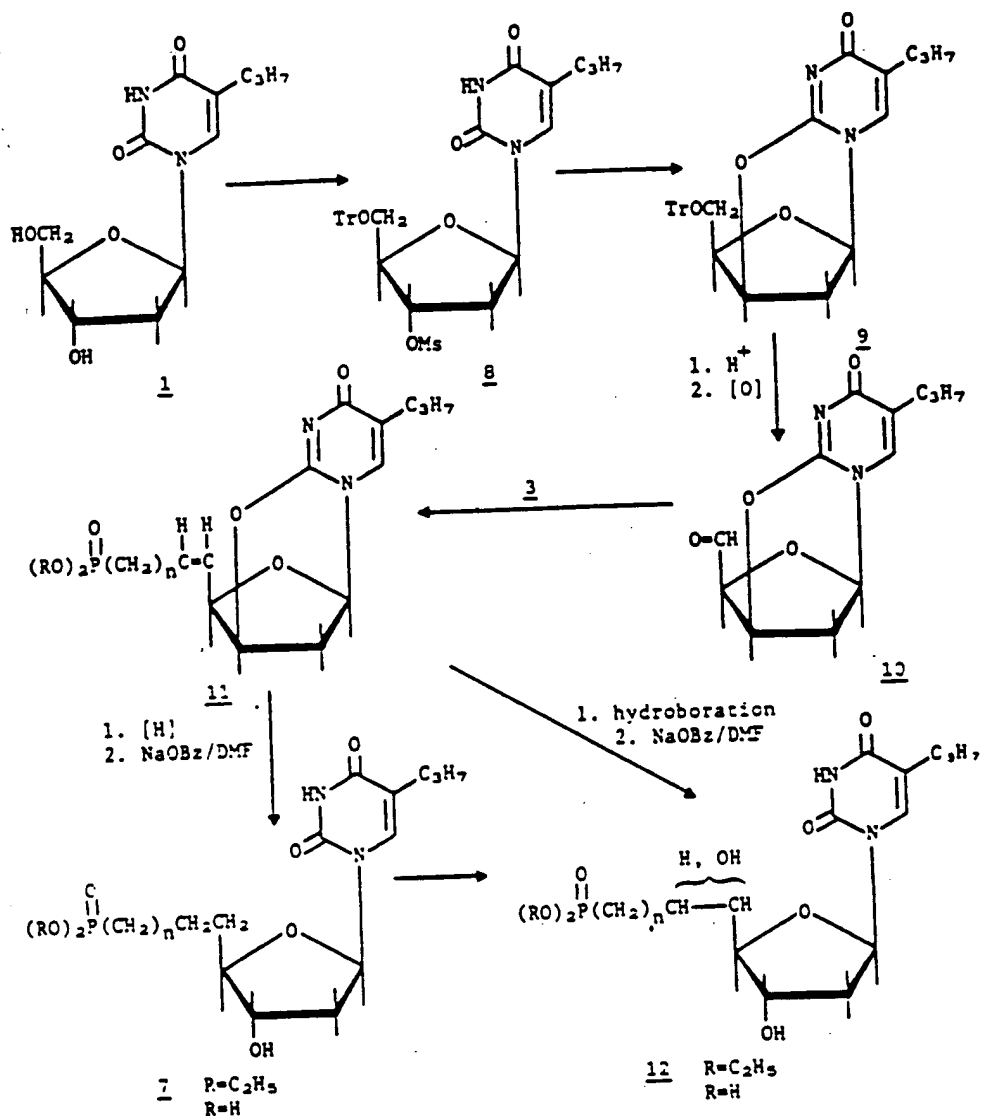
Oxidation of 2',3'-O-isopropylidene-5-propyluridine (1) by the Moffatt procedure, Pfitzner  
10 and Moffatt J Am Chem Soc, 85 3027 (1963) will yield the 5'-aldehyde. The reaction of (2) by the Wittig reagent prepared as shown in Scheme (2) gives the chain-extended, unsaturated "nucleotide" (4). Hydrogenation and deacetonation of the nucleotide (4) will  
15 give the partially unblocked nucleotide (5).

The conversion of the riboside (5) to the deoxyriboside (7) is accomplished by a strategy described recently by Lessor and Leonard, J Org Chem, 46 4300 (1981), which was based on the selective partial  
20 deacylation of fully acylated nucleosides outlined by Ishido, et al, J Chem Soc, Perk I, 563 (1980). Thus benzoylation of (5) to the 2',3'-di-O-benzoate followed by treatment with hydroxylaminium acetate in dry pyridine will give the 3'-benzoate (6). Thiobenzoylation of (6) followed by treatment with tributyl tin  
25 and debenzoylation using sodium benzyloxide, converts the 2'-hydroxyl to H, deacylates the 3'-O-benzoate, and substitutes the phenyl phosphate ester with benzyl phosphate, Jones and Moffatt J Am Chem Soc, 90 5337  
30 (1968). Hydrogenolysis removes the benzyl ester and gives the desired phosphonic acid (7).

Alternatively, compounds in the 2-deoxy-  
ribose series are prepared from the 2'-deoxynucleoside  
by chemistry outlined in Scheme III. Thus, selective  
tritylation followed by mesylation of 5-propyl-2'-  
5 deoxyuridine (1) gives (8), which is converted to the  
2,3'-cyclonucleoside (9) using sodium benzoate in DMF  
(Yung and Fox, J Am Chem Soc, 83 3060 (1961)). Oxida-  
tion to the aldehyde (10) followed by a Wittig conden-  
sation gives the unsaturated phosphonate (11). Hydro-  
10 genation and ring-opening (Yung and Fox) gives the  
phosphonate ester (7), which can be deblocked, (U.S.  
Patent 3,524,846 and J Am Chem Soc, 90 5337 (1968)) to  
the free phosphonic acid. Hydroboration of (11) fol-  
lowed by ring mixture of 5'-hydroxy and 6'-hydroxy  
15 isomers.

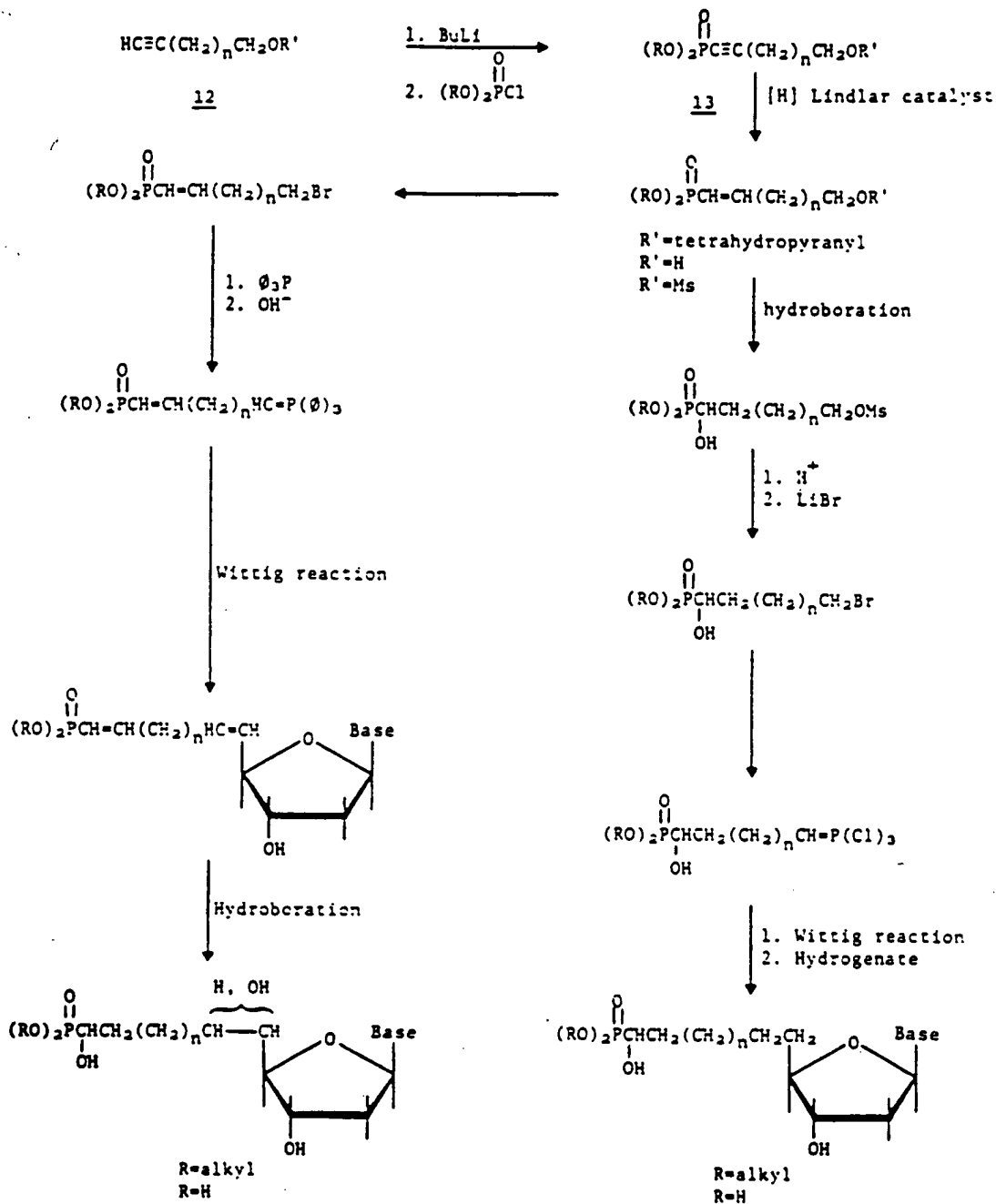
Oxygen functionality  $\alpha$  to the phosphonate  
can be introduced by the chemistry outlined in Scheme  
IV. The appropriate propargyl phosphonic acid (13)  
can be prepared from tetrahydropyranyl-propargyl alco-  
20 hol (12) by the procedures outlined by Chattha and  
Aquiari, J Org Chem, 36 2719-20 (1971). Selective  
hydrogenation to the vinyl phosphonate followed by the  
sequence outlined in Scheme IV results in phosphonate  
analogues with one or two hydroxyls in the phosphonate  
25 chain.





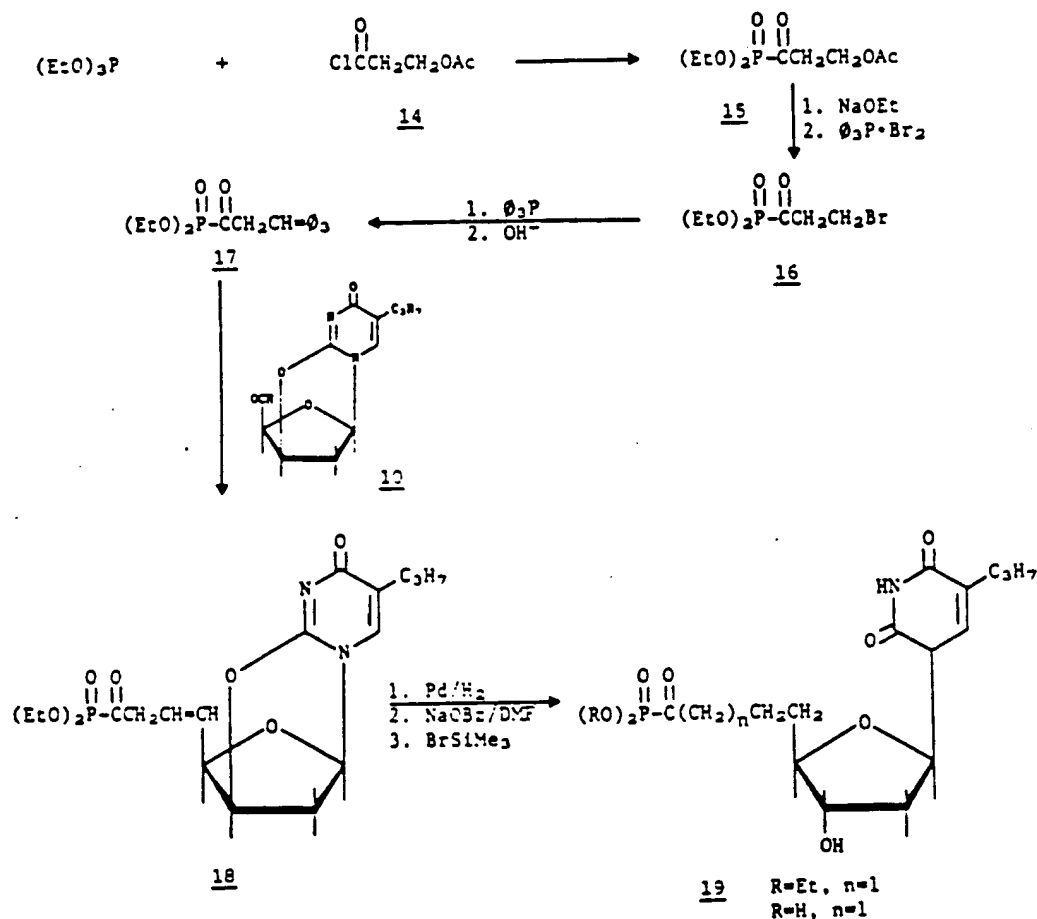
Scheme III

doesn't say how  
make the purines



### Scheme IV

Carbonyl analogs can be prepared by the chemistry outlined in Scheme V. This method involves Arbuzov reaction of triethylphosphite with  $\beta$ -acetoxypropionyl chloride (14) by the method of Yamashita, et al, Bull Chem Soc Japan, 53(6) 1625 (1980).

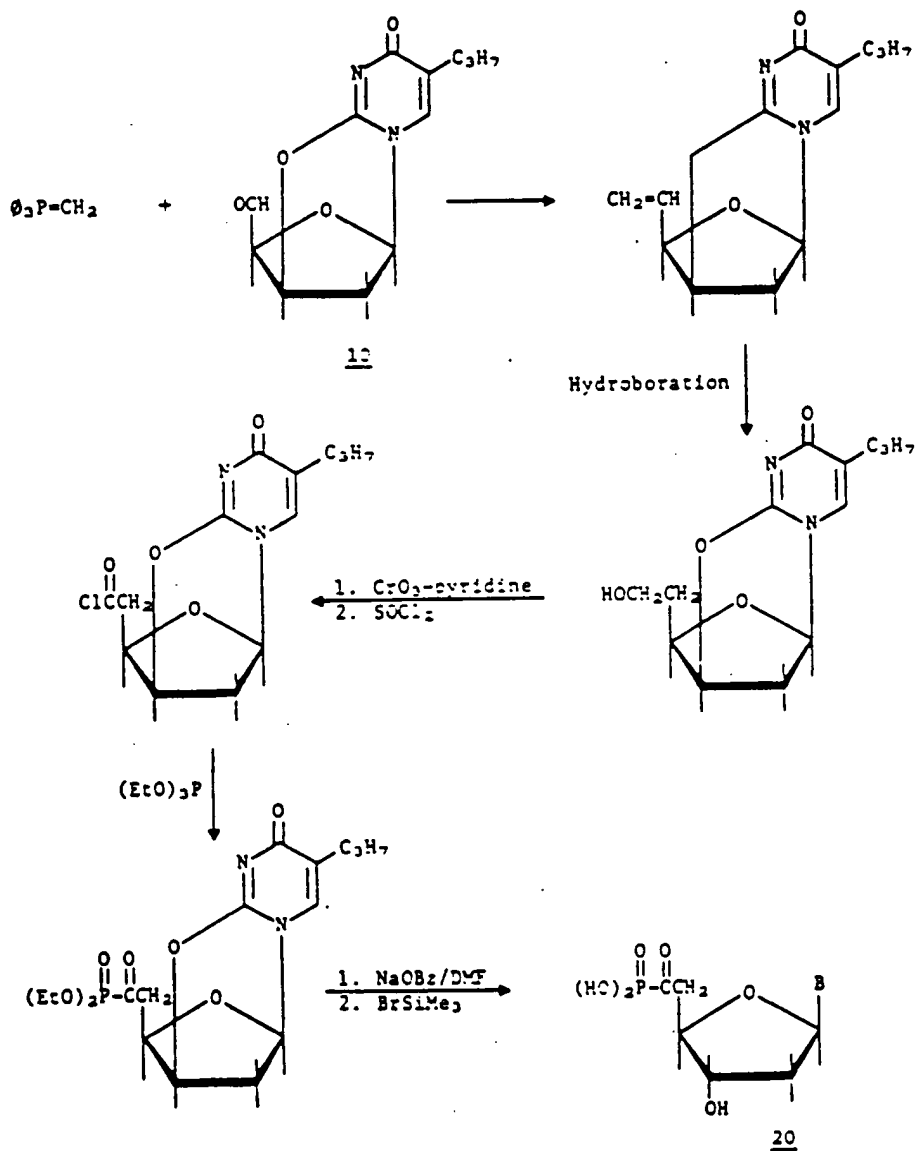


Scheme V

- 5 This gives the  $\alpha$ -carbonyl phosphonate ester (15).  
 Conversion of 15 to the bromoethyl derivative 16  
 followed by reaction with triphenylphosphine will give  
 the Wittig reagent (17). Condensation of 17 with the  
 appropriate aldehyde (e.g. 10) gives the olefin 18,  
 10 which, after hydrogenation and deblocking, results in

the desired product 19, a nucleoside diphosphonate analog. The nucleoside triphosphate analog 19 (wherein  $n = 3$ ) can be prepared starting from 5-acetoxyvalerylchloride.

5 The nucleoside monophosphonate analog (20) can be prepared by the chemistry outlined in Scheme VI.



Scheme VI



### Salts

Physiologically acceptable salts of compounds of this invention are prepared by methods known in the art. The salts include ammonium salts and  
5 salts of physiologically acceptable metals, particularly  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ , and are novel compounds and comprise a further aspect of the invention. Metal salts can be prepared by reacting a metal  
10 hydroxide with a compound of the invention. Examples of metal salts which can be prepared in this way are salts containing  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ . A less soluble metal salt can be precipitated from a solution of a more soluble salt by addition of a suitable metal compound. Acid salts can be prepared by reacting a compound  
15 of the invention with an acid such as  $\text{HCl}$ ,  $\text{HBr}$ ,  $\text{H}_2\text{SO}_4$ , or an organic sulphonic acid.

### Pharmaceutical Preparations

The compounds of this invention (including the physiologically acceptable salts thereof) have  
20 antiviral activity. They present activity against Herpes Simplex viruses and related viruses for example Herpes Simplex virus I, Herpes Simplex virus II, Epstein-Barr virus, varicella Zoster virus, and cytomegalo virus. Thus the compounds can be formulated  
25 into pharmaceutical preparations. Such preparations are composed of one or more of the compounds in association with a pharmaceutically acceptable carrier. The book Remington's Pharmaceutical Sciences, 15th Ed by E.W. Martin (Mark Publ. Co., 1975) discloses typical  
30 carriers and methods of preparation, which disclosure is incorporated by reference.

The compounds may be administered topically, orally, parenterally (e.g. intravenously, by

intramuscular injection, or by intraperitoneal injection or the like depending upon the nature of the viral infection being treated.

For internal infections the compositions  
5 are administered orally or parenterally at dose levels of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight and can be used in man in a unit dosage form administered one to four times daily in the amount of 1 to 250 mg per unit dose. For oral  
10 administration, fine powders or granules may contain diluting, dispersing and/or surface active agents, and may be presented in water or in a syrup, in capsules or sachets in the dry state or in a nonaqueous solution or suspension, wherein suspending agents may be  
15 included; in tablets, wherein binders and lubricants may be included, or in a suspension in water or a syrup. Where desirable or necessary, flavoring, preserving, suspending, thickening or emulsifying agents may be included. Tablets and granules are preferred  
20 oral administration forms and these may be coated.

For parenteral administration or for administration as drops, as for eye infections, the compounds may be presented in aqueous solution in a concentration of from about 0.1 to 10%, more preferably  
25 about 0.1 to 7%. The solution may contain antioxidants, buffers, etc.

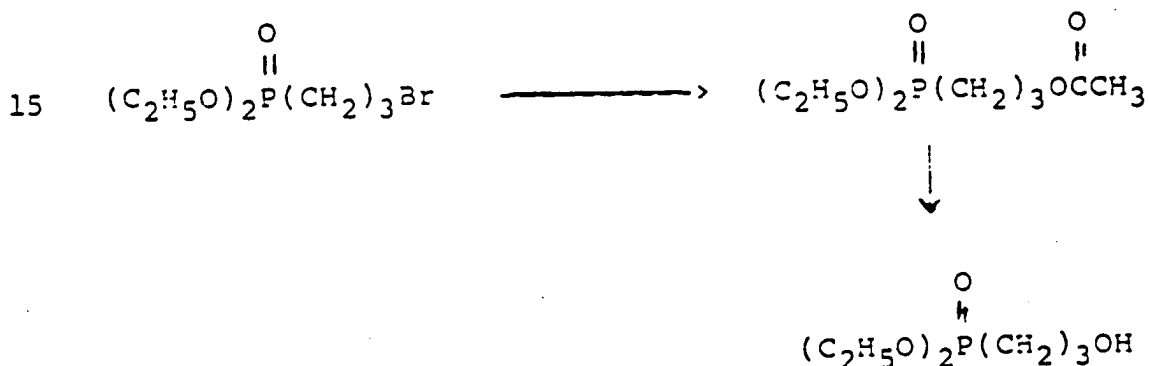
Alternatively, for infections of the eye, or other external tissues, e.g. mouth and skin the compositions are preferably applied to the infected  
30 part of the body of the patient topically as an ointment, cream, aerosol or powder, preferably as an ointment or cream. The compounds may be presented in an ointment, for instance with a water soluble ointment base, or in a cream, for instance with an oil in water

cream base in a concentration of from about 0.01 to 10%, preferably 0.1 to 7%, most preferably about 0.5% w/v. Additionally, viral infections of the eye, such as Herpetic keratitis may be treated by use of a sustained release drug delivery system as is described in the art.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgement of the attending practitioner.

The invention will be further described by the following nonlimiting examples.

Example I



Diethyl-3-hydroxypropylphosphonate

Diethyl-3-bromophosphonate (12.0 g, 46 mmol, prepared by the method of Anatol Eberhard and F.H. Westheimer, JACS 87 253-260 (1965)) was stirred with 12.0 g NaOAc·3H<sub>2</sub>O in 125 ml DMF heated in a steam bath. The reaction was evaporated to dryness in vacuo after 2 hours and partitioned between H<sub>2</sub>O and EtOAc, extracting the aqueous layer five times. The ethyl acetate extract was washed once with brine, dried with

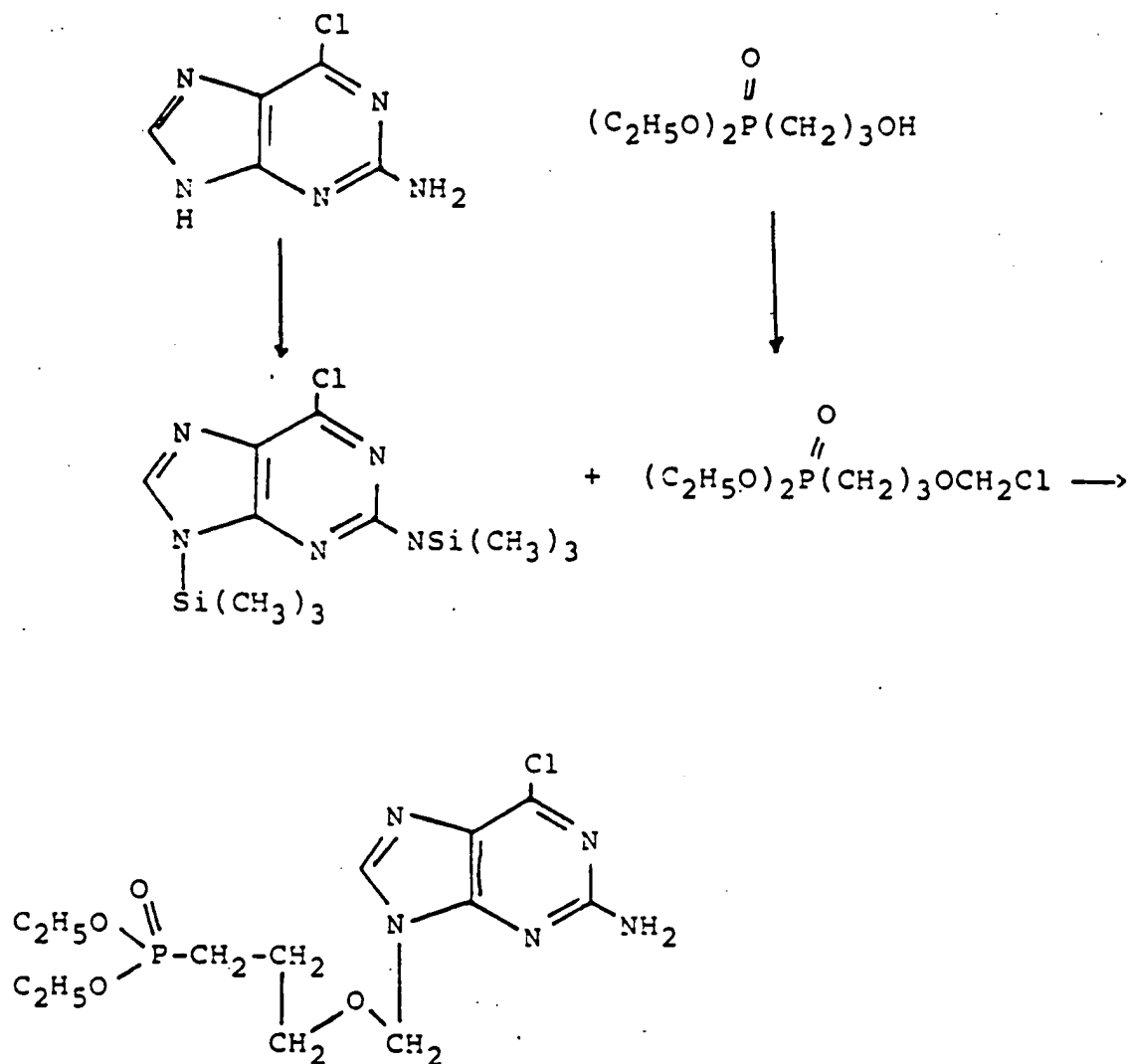
Na<sub>2</sub>SO<sub>4</sub>. filtered, and evaporated to dryness in vacuo to yield 9.8 g light yellow oil (89%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.3 (tr, 6 H), 1.5-2.0 (m, 4 H), 2.03 (s, 3 H), 4.1 (assym. quintet, 6 H). thin layer chromatography on  
5 SiGF developed with 2:1 EtOAc:CH<sub>2</sub>Cl<sub>2</sub> gave R<sub>f</sub> 0.30. The isolated diethyl-3-acetoxypropylphosphonate (9.8 g, 41 mmol) in 200 ml abs. EtOH was stirred with 30 ml Dowex 50 (H<sup>+</sup>) which had been rinsed three times each with H<sub>2</sub>O and EtOH. After 4-1/2 days at room  
10 temperature, another 10 ml of similarly prepared resin was added. Six hours later, the reaction was filtered and evaporated in vacuo. The quantitative yield of yellow oil was purified by dry column chromatography on 400 g silica packed in a 2.75 inch flat diameter  
15 nylon tube. The column was eluted with 1:9 MeOH:EtOAc and the appropriate fractions were cut and slurried with 1:1 MeOH:EtOAc. Filtration and evaporation in vacuo afforded 5.33 g (66%) pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub> D<sub>2</sub>O): δ 1.30 (tr, 6 H), 1.60-2.08 (m, 4 H),  
20 3.67 (tr, 2 H), 4.13 (quintet, 4 H); thin layer chromatography on SiGF developed with 1:9 MeOH:EtOAc gave an R<sub>f</sub> of 0.57.

9(3-phosphono-1-propyloxymethyl)guanine

To 9.40 mmol silylated guanine (James L.  
25 Kelley, Mark P. Krochmal, and Howard J. Shaeffer, J Med Chem, 24 1528-1531 (1981)) in 9 ml dry toluene was added 7.60 mmol diethyl-3-chloromethoxypropylphosphonate, prepared from diethyl-3-hydroxypropylphosphonate according to the procedure of Kelley, et al,  
30 followed by the addition of 2.2 ml triethylamine. The reaction was refluxed 24 hours and evaporated to dryness in vacuo. The residue was digested with 70 ml EtOH and the voluminous tan solid was isolated by suc-

tion filtration. The solid was dissolved in water, made basic with conc.  $\text{NH}_4\text{OH}$ , and treated with excess aqueous lead diacetate. The lead salt was isolated by centrifugation and dissolved in 50% acetic acid followed by treatment with  $\text{H}_2\text{S}$  for 20 minutes. The black lead sulfide was removed by suction filtration through Celite. The filtrate was evaporated to dryness in vacuo, triturated in EtOH, and filtered. The residue was further triturated in DMF and filtered to yield 320 mg off-white solid. This solid was dissolved in minimum water, acidified with 1 M HCl. Thereafter it was neutralized with 1 M NaOH and lyophilized. The solid residue was triturated in a mixture of DMF,  $\text{H}_2\text{O}$ , and EtOH and filtered to yield 276 mg of 9(3-phosphono-1-propyloxymethyl) guanine as a white solid (8.3%). Anal. ( $\text{C}_9\text{H}_{12}\text{N}_5\text{O}_5\text{P} \cdot 2\text{Na} \cdot 5\text{H}_2\text{O}$ ) C, H, N; UV  $\gamma_{\text{max}}$  ( $\epsilon$ ): pH 1, 255 (14, 700); pH 7, 251 (15, 600); pH 11, 257 (12, 800), 267 (12, 800); mass spectrum (TMS derivative) m/e 591 ( $\text{M}^+$  of  $\text{TMS}_4$  derivative);  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ):  $\delta$  1.25-1.90 (m, 4 H), 3.42 (tr, 2 H), 5.50 (s, 2 H), 7.92  $\delta$  (s, 1 H). Thin layer chromatography on SiGF developed with 7:3  $\text{CH}_3\text{CN}$ :0.1 N  $\text{NH}_4\text{Cl}$  gave  $R_f$  0.20.

Example II



5 6-Chloro-9(3-diethylphosphono-1-propyloxy-methyl)guanine

To 0.5 g (2.95 mmol) 2-amino-6-chloropurine, silylated and treated with  $\text{Hg}(\text{CN})_2$  according to the procedure of Robins and Hatfield (Morris J. Robins and  
 10 Peter W. Hatfield, Can J Chem, 60 547-553 (1982)) in 40 ml benzene was added a solution of 2.68 mmol

diethyl-3-chloromethoxypropylphosphonate prepared from (0.525 g) diethyl-3-hydroxypropylphosphonate according to the procedure of Kelley, et al, (James L. Kelley, Mark P. Krochmal and Howard J. Shaeffer, J Med Chem, 5 24 1528-1531 (1981)). The reaction was refluxed for 2 hours, cooled and 400 ml  $\text{CHCl}_3$  was added. The organic phase was washed successively with 80 ml each of aqueous saturated  $\text{NaHCO}_3$  and 1 M aqueous KI. The organic solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to 790 mg of yellow gum. A portion of this crude material was used to conduct hydrolysis experiments. The remaining material was chromatographed on a silica column. A solution of 574 mg of the crude reaction product was placed on 20 g silica packed in a column using 5:3 EtOAc:nPrOH. Elution with the same mixed solvent afforded sixteen fractions of 10-20 ml each. Fractions 7-12 were combined to yield 258 mg of a colorless oil which spontaneously crystallized. Trituration in  $\text{CH}_2\text{Cl}_2 \cdot \text{Et}_2\text{O}$  afforded two crops of white solid (207 mg), mp 109-110° (28%). A yield of 46% was obtained from a reaction performed on 45.2 mmol of the starting purine. Anal ( $\text{C}_{13}\text{H}_{21}\text{ClN}_5\text{O}_4\text{P}$ )  $\text{C}_{13}\text{H}_{21}\text{N}$ ; UV  $\gamma_{\text{max}}$  ( $\epsilon$ ): pH 1, 246 ( $\epsilon$  6600), 310 (7200); pH 7, 247 (6800), 308 (7400); pH 11 247 (6600), 308 (7100); mass spectrum: m/e 377 ( $\text{M}^+$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.3 (tr, 6 H), 1.52-2.18 (m, 4 H), 3.58 (tr, 2 H), 4.09 (qu, 4 H), 5.48 (s. with broad base, 4 H), 7.89 (s, 1 H). Thin layer chromatography on SiGF developed with 5:3 EtOAc:nPrOH gave  $R_f$  0.40.

30 9(3-ethylphosphono-1-propyloxymethyl)guanine

6-Chloro-9(3-diethylphosphono-1-propyloxy-methyl)guanine (75 mg; 0.2 mmol) was combined with 5 ml 1 N aqueous NaOH and refluxed 1 hour. The cooled



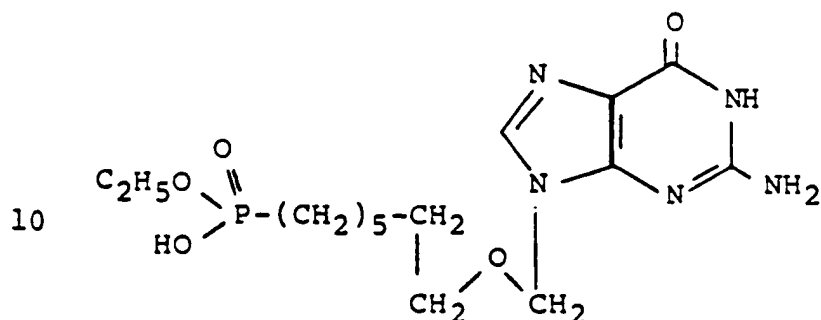
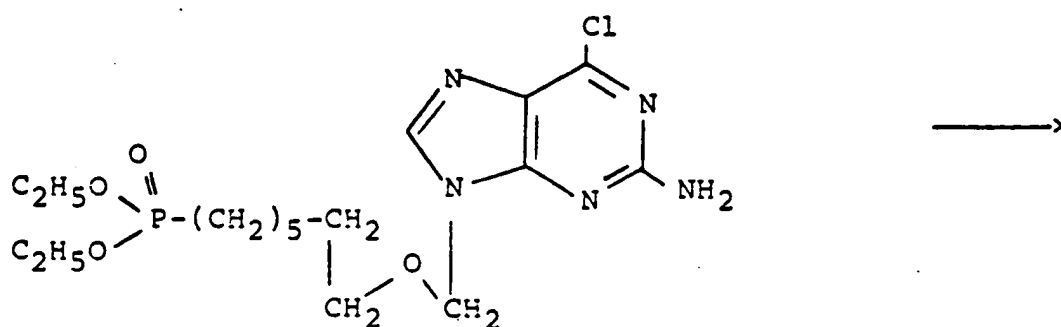
reaction was neutralized with Dowex 50X8 (pyridinium form) and filtered, rinsing liberally with water. The solution was partially evaporated to remove pyridine and was then lyophilized. The orange-colored residue (74 mg) was redissolved in H<sub>2</sub>O and centrifuged to remove insoluble material. The decanted solution (2 ml) was chromatographed on a 0.9 x 46 cm column of Whatman DE-52 Cellulose, HCO<sub>3</sub> form, using a linear gradient of one liter each H<sub>2</sub>O and 0.2 M NH<sub>4</sub>HCO<sub>3</sub> after an initial H<sub>2</sub>O elution. Fractions (7 ml each) 43-47 yielded 25 mg (36%) of fluffy white solid after three lyophilizations. Electron impact mass spectrum (TMS derivative) showed m/l 547 (M<sup>+</sup> of TMS derivative); chemical ionization mass spectrum (TMS derivative) showed m/l 549 (M<sup>+</sup> + H of TMS<sub>3</sub> derivative). <sup>1</sup>H NMR (D<sub>2</sub>O) showed δ 1.19 (tr, 3 H), 1.4-1.9 (m, 4H), 3.59 (tr, 2 H), 3.90 (quintet, 2 H), 5.47 (s, 2 H), 8.2 (br's, 1 H). Thin layer chromatography behavior on SiGF: R<sub>f</sub> 0.40 when developed with 7:3 CH<sub>3</sub>CH. 0.1 N aqueous NH<sub>4</sub>Cl. The material had a formula of (C<sub>11</sub>H<sub>18</sub>N<sub>5</sub>O<sub>5</sub>P·H<sub>2</sub>O) Calc: C-37.82% H-5.77%, N-20.0. Found: C-38.27%, H-5.84%, N-19.65%. A UV spectrum was run on the material and showed UV γ<sub>max</sub> (ε): pH 1, 256 (10, 400), 278 shoulder; pH 7, 252 (11, 300) 271 shoulder; pH 11, 256-258 (9, 600) 267 shoulder. The product was relyophilized.







a colorless gum. UV  $\gamma_{\max}$  pH 1: 246 nm ( $\epsilon$  6220), 310 nm ( $\epsilon$  6380);  $\gamma_{\max}$  pH 7, 247 nm ( $\epsilon$  5910), 310 nm ( $\epsilon$  6410);  $\gamma_{\max}$  pH 11, 246 nm ( $\epsilon$  5950), 309 nm ( $\epsilon$  6380); mass spectrum  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.1-1.9 (m, 18 H), 3.48 (t, 2 H), 4.10 (q, 4 H), 5.47 (s, 2 H), 5.88 (s, 2 H), 7.93 (s, 1 H). Thin layer chromatography on silica gel GF gave  $R_f$  0.15 using ethylacetate:ethanol (100:1).



9-(7-ethylphosphono-1-heptyloxymethyl)guanine:

6-chloro-9(7-diethylphosphono-1-heptyloxy-methyl)guanine was hydrolyzed by refluxing 1 N aqueous sodium hydroxide for 4 hours and isolated in 30% yield as described for the preparation of 9-(3-ethylphosphono-1-propyloxymethyl)guanine (Example II). It had  $R_f$  0.5 on silica gel GF using acetonitrile (7:3) 0.1 N aqueous ammonium chloride. Proton NMR ( $\text{D}_2\text{O}$ ) 1.1-1.5 (m, 15 H), 3.5 (t, 2 H), 3.90 (q, 2 H), 5.45 (s, 2 H) UV.

### Biological Testing

The compounds of Example I and II were evaluated in vitro as antiviral agents against herpes virus.

5           The virus strain employed was Strain McCrae of type 1 herpes (thymidine kinase positive virus) prepared and titered in MA-104 cells and frozen at -90°C until use.

10           Continuous passaged monkey kidney (MA-104) cells were used, with growth medium consisting of Minimum Essential Medium (MEM) supplemented with 0.1% NaHCO<sub>3</sub> and 9% fetal calf serum. Test medium consisted of MEM supplemented with 2% fetal bovine serum, 0.18% NaHCO<sub>3</sub> and 50 µl gentamicin.

15           The last compounds were added to test medium at a concentration of 2000 µg/ml for use as a positive control.

### Antiviral Test Method

20           To a 96 well microtiter plate containing an established 24 hour monolayer of cells from which the medium has been decanted was added 0.1 ml of varying (one-half log<sub>10</sub>) concentrations of test compound, which incubated on the cell 15 minutes, after which 0.1 ml of virus in a concentration of 320 cell culture  
25 50% infectious doses (CCID<sub>50</sub>)/0.1 ml was added. The plate was covered with plastic wrap and incubated at 37°C. Included with the test were toxicity controls (each concentration of compound + test medium in place of virus), virus controls (virus + test medium in  
30 place of compound) and cell controls (test medium in place of compound and virus). The cells were examined microscopically after 72 hours for evidence of cytotoxicity and for viral cytopathic effect (CPE). Vidarabine was run on the same plate in parallel.



Antiviral activity was determined by observation of inhibition of viral CPE. This activity was expressed by minimum inhibitory concentration (MIC), defined as that dose range of compound causing 50% CPE inhibition. A Virus Rating (VR) was also determined, which is a numerical expression of antiviral activity, weighted to take into account any cytotoxicity observed. Generally, a VR of 0.1 - 0.4 is usually indicative of slight antiviral effect, 0.5 - 0.9 indicates moderate antiviral effect, and >1.0 implies strong antiviral activity.

The results of these are summarized in tables A and B. The test compound had a strong activity against the thymidine kinase positive type I herpes virus. The activity was considered equivalent to that of vidarabine.

TABLE A

Effect of compound of Example I and Vidarabine  
on Thymidine Kinase-Positive Type 1 Herpes Virus  
Infections in MA-104 Cells

<u>Compound of I</u>		<u>Vidarabine</u>	
	CPE <sup>a</sup>		CPE <sup>a</sup>
Conc.	Inhib.	Conc.	Inhib.
( $\mu$ g/ml)	(%)	( $\mu$ /ml)	(%)
5	1000	100	100
	320	320	100
	100	100	87
	32	32	87
	10	10	69
10	3.2	3.2	28
	1.0	1.0	56
	0	0	
	VR <sup>b</sup>	1.4	1.3
	MIC <sup>c</sup>	10	10

15 <sup>a</sup>Cytopathic effect, % cell alteration or destruction.

<sup>b</sup>Virus rating, a numerical expression of antiviral activity (Sidwell et al, Appl Microbiol, 22:797, (1971), 0.1 - 0.4 = slight activity, 0.5 - 0.9 = moderate activity,  $\geq$  1.0 = strong activity.

<sup>c</sup>Minimum inhibitory concentration - that dosage range wherein a 50% CPE inhibition is seen.

TABLE B

Effect of compound of Example II and Vidarabine  
on Thymidine Kinase Positive Type 1 Herpes Virus  
in MA-104 Cells (Two Tests)

	Compound of II			Vidarabine (Control)		
	Conc. ( $\mu$ g/ml)	Test1 CPE <sup>a</sup> Inhib. (%)	Test2 CPE <sup>a</sup> Inhib. (%)	Conc. ( $\mu$ /ml)	Test1 CPE <sup>a</sup> Inhib. (%)	Test2 CPE <sup>a</sup> Inhib. (%)
5	1000	100	76	1000	100	100
	320	82	67	320	100	100
	100	47	57	100	96	85
	32	6	57	32	96	57
	10	38	48	10	60	39
10	3.2	96	52	3.2	2	0
	1.2	69	48	1.0	0	0
	0			0		
	VR <sup>b</sup>	>2.0	>1.4	VR <sup>b</sup>	0.8	07
	MIC <sup>c</sup>	<1.0	<1.0	MIC <sup>c</sup>	10	10
15	MTD <sup>d</sup>	320	>1000		10	10

<sup>a</sup>Cytopathic effect, % cell alteration or destruction.

<sup>b</sup>Virus rating, a numerical expression of antiviral activity (Sidwell et al, Appl Microbiol 22:797, (1971), 0.1 - 0.4 = slight activity, 0.5 - 0.9 = moderate activity, > 1.0 = strong activity.

<sup>c</sup>Minimum inhibitory concentration - that dosage range wherein a 50% CPE inhibition is seen,  $\mu$ g/ml.

<sup>d</sup>Maximum tolerated dose,  $\mu$ g/ml.

The compound of Example II was further evaluated by the above-described in vitro test method against cytomegalo virus. The compound was strongly active with a VR of 2.1-2.3.

5           The compound of Example II was tested in vivo in guinea pigs as an agent against thymidine kinase positive herpes virus. The animals were inoculated with the virus. Eighteen hours later the material of Example II (0.4% solution in water or 1-2% solution), a 5% solution of acyclovir or a 1.4% solution of poly(vinylalcohol) was administered and 10           five days later blister diameters at the point of inoculation were measured. Satellite lesions were measured as well.

20           The results of these tests are given in Table C and show that the compound has superior activity against TK<sup>+</sup> virus.

TABLE C

Effect of Compound of Example II  
in vivo against Herpes Virus

25	Virus	Placebo, 1.4%	Acyclovir,	Cx of II	Cx of II
		<u>poly(vinylalcohol)</u>	<u>5%</u>	<u>1-2%*</u>	<u>0.4%</u>
	TK <sup>+</sup>	1.7**	1.0	0.9	2.1
	Satellite				
	lesions	9	4	6	11

\*saturated solution

30   \*\*average number of lesions

Formulations

The following formulations based on the compounds of the invention and their preparation are representative.

5           A formulation suitable for injections intramuscularly or intraperitoneally is prepared by combining the first four of the following materials

Compound of the Invention	1 gram
Poly(ethylene glycol)	50 grams
10       Propylene glycol	50 grams
Tween 80 suspension agent	1.5 grams
Injectable Saline	200 ml

and then adding the last material. The material forms a clear solution which is filtered and sealed in sterile  
15       containers.

A simple intravenous injection formulation is formed by dissolving 1 gram of an active compound in 250 ml of injectable saline which after filtering is packaged in sterile bottles.

20           A cream for topical administration is formulated by stirring 10 g of active compound of the invention with 20 g of mineral oil, 40 g of petroleum jelly, 0.3 g of mixed methyl/propyl paraben and 5 g of nonionic surfactant at 50°C. Then 150 ml of water are  
25       stirred into the mixture at 50°C at high speed to form a cream and the mixture is cooled and packaged in capped tubes.

An oral dosage form is prepared from 10 g of compound of the invention, 100 g of lactose, and 1 g of  
30       starch which are mixed with 0.1 g of magnesium stearate in methanol to granulate. The methanol is removed by gentle heating with stirring. A portion of this material is retained as a granular powder for oral use while the remainder is hand formed into 250 mg tablets  
35       in a manual tableting machine.

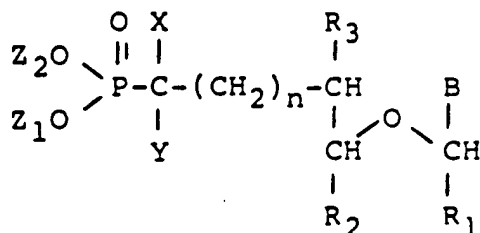


The foregoing examples and formulations have been presented to illustrate the present invention and are not to be construed as limitations on the invention's scope which is instead defined by the following  
5 claims.



What is Claimed is

1. A compound having the structure



- wherein  $Z_1$  and  $Z_2$  are the same or different and selected from the group made up of hydrogen, the one to six carbon alkyls, phenyl and benzyl, X is H, OH, or together with  $Y = O$ , Y is H or together with  $X = O$ , n is an integer, 0, 2 or 4,  $R_1$  and  $R_2$  together complete a  $\beta$ -pentofuranose sugar or  $R_1$  is H and  $R_2$  is H or  $-\text{CH}_2\text{OH}$ ,  $R_3$  is H or OH and B is a purine or pyrimidine base.

2. The compound of claim 1 wherein  $R_1$  and  $R_2$  together complete a  $\beta$ -pentofuranose sugar.

3. The compound of claim 2 wherein B is selected from guanine, adenine, 5-iodouracil, 5-trifluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil, 5-propyluracil and 5-ethyluracil.

4. The compound of claim 2 wherein n is 0.

5. The compound of claim 2 wherein n is 2.

6. The compound of claim 2 wherein n is 4.

7. The compound of claim 2 wherein the  $\beta$ -pentofuranose is a  $\beta$ -ribofuranose.



8. The compound of claim 2 wherein the  $\beta$ -pentofuranose is a  $\beta$ -arabinofuranose.

9. The compound of claim 2 wherein  $Z_1$  and  $Z_2$  are each selected from the group made up from hydrogens  
5 and one to four carbon alkyls.

10. The compound of claim 9 wherein  $n$  is 0.

11. The compound of claim 9 wherein  $n$  is 2.

12. The compound of claim 9 wherein  $n$  is 4.

13. The compound of claim 2 wherein  $X$  and  $Y$   
10 are each hydrogens.

14. The compound of claim 2 wherein  $X$  and  $Y$  together are =0.

15. The compound of claim 2 wherein  $X$  is hydroxyl and  $Y$  is hydrogen.

16. The compound of claim 1 wherein  $R_1$  is  
15 hydrogen and  $R_2$  is hydrogen.

17. The compound of claim 16 wherein  $B$  is selected from guanine, adenine, 5-iodouracil, 5-tri-fluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil,  
20 5-propyluracil and 5-ethyluracil.

18. The compound of claim 16 wherein  $Z_1$  and  $Z_2$  are each selected from the group made up of hydrogen and one to four carbon alkyls.



19. The compound of claim 18 wherein X and Y are each hydrogens.

20. The compound of claim 18 wherein X and Y together are =0.

5           21. The compound of claim 18 wherein X is hydroxyl and Y is hydrogen.

22. The compound of claim 19 wherein n is 0.

23. The compound of claim 19 wherein n is 2.

24. The compound of claim 19 wherein n is 4.

10           25. The compound of claim 1 wherein  $R_1$  is hydrogen and  $R_2$  is hydroxymethyl.

26. The compound of claim 25 wherein B is selected from guanine, adenine, 5-iodouracil, 5-tri-fluorothymine, 5-iodocytosine, E-5-2-bromovinyluracil,  
15 5-propyluracil and 5-ethyluracil.

27. The compound of claim 25 wherein  $Z_1$  and  $Z_2$  are each selected from the group made up of hydrogen and one to four carbon alkyls.

28. The compound of claim 27 wherein X and Y  
20 are each hydrogens.

29. The compound of claim 27 wherein X and Y are =0.



30. The compound of claim 27 wherein X is hydroxyl and Y is hydrogen.

31. The compound of claim 28 wherein n is 0.

32. The compound of claim 28 wherein n is 2.

5 33. The compound of claim 28 wherein n is 4.

34. A metal salt of a compound of claim 1.

35. A pharmaceutical preparation comprising a compound of claim 1 in a pharmaceutically acceptable carrier.

10 36. A method for treating herpes in a mammal in need of such treatment comprising administering to said mammal an effective herpes-treating dose of the preparation of claim 35.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 84/00737

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>3</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>3</sup> : C 07 H 19/10; C 07 H 19/20; C 07 F 9/65; A 61 K 31/00; A 61 K 31/675																							
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched <sup>4</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px; vertical-align: top;">IPC<sup>3</sup></td> <td style="padding: 5px; vertical-align: top;">C 07 H 19/00; C 07 F 9/00; A 61 K 31/00</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>4</sup></div>			Classification System	Classification Symbols	IPC <sup>3</sup>	C 07 H 19/00; C 07 F 9/00; A 61 K 31/00																	
Classification System	Classification Symbols																						
IPC <sup>3</sup>	C 07 H 19/00; C 07 F 9/00; A 61 K 31/00																						
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>14</sup></b> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category <sup>*</sup></th> <th style="border-bottom: 1px solid black;">Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup></th> <th style="width: 10%; border-bottom: 1px solid black;">Relevant to Claim No. <sup>18</sup></th> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">X,Y</td> <td style="padding: 5px;">GB, A, 1243213 (SYNTHEX) 18 August 1971 see pages 9-11; pages 20-22 --</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">1-34</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">X,Y</td> <td style="padding: 5px;">DE, A, 2009834 (SYNTHEX) 17 September 1970 see pages 64-73 --</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">1-34</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">X,Y</td> <td style="padding: 5px;">FR, A, 2381781 (WELLCOME) 22 September 1978 see pages 1-5 --</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">1-36</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">X,Y</td> <td style="padding: 5px;">DE, A, 3045375 (ROBUGEN) 1 July 1982 see pages 1-5 --</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">1-36</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">X,Y</td> <td style="padding: 5px;">EP, A, 0074306 (MERCK &amp; CO.) 16 March 1983 see pages 1-11 --</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">1-36</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">X,Y</td> <td style="padding: 5px;">EP, A, 0049072 (EMS BIOLOGICALS) 7 April 1982 see pages 1-13 --</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">1-36 ./.</td> </tr> </table>			Category <sup>*</sup>	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>	X,Y	GB, A, 1243213 (SYNTHEX) 18 August 1971 see pages 9-11; pages 20-22 --	1-34	X,Y	DE, A, 2009834 (SYNTHEX) 17 September 1970 see pages 64-73 --	1-34	X,Y	FR, A, 2381781 (WELLCOME) 22 September 1978 see pages 1-5 --	1-36	X,Y	DE, A, 3045375 (ROBUGEN) 1 July 1982 see pages 1-5 --	1-36	X,Y	EP, A, 0074306 (MERCK & CO.) 16 March 1983 see pages 1-11 --	1-36	X,Y	EP, A, 0049072 (EMS BIOLOGICALS) 7 April 1982 see pages 1-13 --	1-36 ./.
Category <sup>*</sup>	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>																					
X,Y	GB, A, 1243213 (SYNTHEX) 18 August 1971 see pages 9-11; pages 20-22 --	1-34																					
X,Y	DE, A, 2009834 (SYNTHEX) 17 September 1970 see pages 64-73 --	1-34																					
X,Y	FR, A, 2381781 (WELLCOME) 22 September 1978 see pages 1-5 --	1-36																					
X,Y	DE, A, 3045375 (ROBUGEN) 1 July 1982 see pages 1-5 --	1-36																					
X,Y	EP, A, 0074306 (MERCK & CO.) 16 March 1983 see pages 1-11 --	1-36																					
X,Y	EP, A, 0049072 (EMS BIOLOGICALS) 7 April 1982 see pages 1-13 --	1-36 ./.																					
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>*</sup> Special categories of cited documents: <sup>15</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>																							
<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of the Actual Completion of the International Search <sup>1</sup></td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of Mailing of this International Search Report <sup>1</sup></td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">24th October 1984</td> <td style="border-bottom: 1px solid black; padding: 5px;">26 NOV. 1984</td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">International Searching Authority <sup>1</sup></td> <td style="border-bottom: 1px solid black; padding: 5px;">Signature of Authorized Officer <sup>10</sup></td> </tr> <tr> <td style="padding: 5px;">EUROPEAN PATENT OFFICE</td> <td style="padding: 5px;">             G.L.M. Huydenberg         </td> </tr> </table>			Date of the Actual Completion of the International Search <sup>1</sup>	Date of Mailing of this International Search Report <sup>1</sup>	24th October 1984	26 NOV. 1984	International Searching Authority <sup>1</sup>	Signature of Authorized Officer <sup>10</sup>	EUROPEAN PATENT OFFICE	 G.L.M. Huydenberg													
Date of the Actual Completion of the International Search <sup>1</sup>	Date of Mailing of this International Search Report <sup>1</sup>																						
24th October 1984	26 NOV. 1984																						
International Searching Authority <sup>1</sup>	Signature of Authorized Officer <sup>10</sup>																						
EUROPEAN PATENT OFFICE	 G.L.M. Huydenberg																						

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, <sup>16</sup> with Indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No <sup>18</sup>
X,Y	US, A, 3560478 (T. MEYERS) 2 February 1971 see claims 1-6 --	1-34
X,Y	US, A, 3446793 (C. JONES) 27 May 1969 see claims 1-3 --	1-34
X,Y	Journal of Medicinal Chemistry, vol. 22, no. 1, January 1979 J.A. Montgomery et al.: "Phosphonate analogue of 2'-Deoxy-5-fluorouridylic acid", pages 109-111, see pages 109-110 --	1-36
X,Y	Journal of Heterocyclic Chemistry, vol. XI, February, April, June 1974 J.A. Montgomery et al.: "The use of the wittig reaction in the modification of purine nucleosides (1)", pages 211-218, see page 213 --	1-34
X,Y	Journal of the American Chemical Society, vol. 92, no. 18, 9 September 1970 G.H. Jones: "Communications to the editor. Synthesis of Isosteric Phosphonate analogs of some biologically important phosphodiester", pages 5510-5511, see pages 5510-5511 --	1-34
X,Y	Journal of the American Chemical Society, vol. 90, no. 19, 11 September 1968 G.H. Jones et al.: "The Synthesis of 6'-Deoxyhomonucleoside-6'-phosphonic Acids", pages 5337-5338, see pages 5337-5338 --	1-34
X,Y	Liebigs Annalen der Chemie, vol. 1, 1984, Verlag Chemie (Weinheim, DE) J. Hollmann et al.: "Darstellung und Konformationszuordnung einiger 5'-homologer Adenosinderivate", pages 98-107, see page 99 --	1-34
X,Y	Chemical Review, no. 3, June 1977 R. Engel: "Phosphonates as analogues of natural phosphates", pages 349-367, see page 351 --	1-34
X,Y	Biochemistry, vol. 12, no. 9, 24 April 1973; A. Hampton et al.: "Synthesis of homoadenosine-6'-phosphonic acid and studies of its substrate and	./.

## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No <sup>18</sup>
	<p data-bbox="516 281 1224 394">inhibitor properties with adenosine monophosphate utilizing enzymes", pages 1730-1736, see page 1732</p> <p data-bbox="760 428 883 449">-----</p>	<p data-bbox="1284 348 1360 382">1-36</p>



## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>10</sup>

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out <sup>13</sup>, specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>11</sup>

This International Searching Authority found multiple inventions in this International application as follows:

- claims 1-8, 34-36
- claims 1-8, 34-36
- claims 9-36
- claims 9-36

For explanation: see Form PCT/ISA/210  
supplemental sheet 3

1. ☒ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM Form PCT/ISA/210 - supplemental sheet 2

- 1-8,34-36 : Compounds of the formula on page 40 with R1 and R2 completing a pentofuranose ring and B being a purine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations
- 1-8,34-36 : Compounds of the formula on page 40 with R1 and R2 completing a pentofuranose ring and B being a pyrimidine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations
- 9-36 : Compounds of the formula on page 40 with R1:H and R2H or CH<sub>2</sub>OH and B being a purine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations
- 9-36 : Compounds of the formula on page 40 with R1:H and R2H or CH<sub>2</sub>OH and B being a pyrimidine base, pharmaceutical preparations containing them and a method for treating herpes using those preparations

---

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/11/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1243213	18/08/71	GB-A- 1243214	18/08/71
		DE-A- 1768944	05/01/72
		CH-A- 537392	13/07/73
		US-A- 3662031	09/05/72
		US-A- 3878194	15/04/75
DE-A- 2009834	17/09/70	FR-A- 2034785	18/12/70
		GB-A- 1301182	29/12/72
FR-A- 2381781	22/09/78	NL-A- 7802111	28/08/78
		BE-A- 864316	24/08/78
		DE-A- 2808096	31/08/78
		LU-A- 79126	17/10/78
		JP-A- 53108999	22/09/78
		AT-B- 353286	12/11/79
		AU-A- 3356078	30/08/79
		CA-A- 1094062	20/01/81
		GB-A- 1590500	03/06/81
		US-A- 4287188	01/09/81
		AU-B- 521577	22/04/82
		SE-A- 7802140	25/08/78
		SE-B- 430507	21/11/83
		CH-A- 643858	29/06/84
		AT-B- 366055	10/03/82
DE-A- 3045375	01/07/82	None	
EP-A- 0074306	16/03/83	AU-A- 8755282	03/03/83
		JP-A- 58077881	11/05/83
EP-A- 0049072	07/04/82	JP-A- 57085373	28/05/82
		AU-A- 7527381	25/03/82
		US-A- 4347360	31/08/82
US-A- 3560478	02/02/71	None	
US-A- 3446793	27/05/69	None	

For more details about this annex :  
see Official Journal of the European Patent Office, No. 12/82